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SUMMARY RESULTS OF RESEARCH DIRECTED TOWARD ELICITING EFFECTS OF EXPOSURE TO CARBON MONOXIDE ON THE SPONTANEOUS ELECTROENCEPHALOGRAM AND VISUAL EVOKED CORTICAL ELECTRICAL ACTIVITY

Medical College of Wisconsin

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5. Abstracts

The spontaneous electroencephalogram (EEG) and the visual evoked cortical electrical activity (visual evoked response, VER) were studied in young adult males to ascertain the effects of exposure to carbon monoxide (CO). The EEG was found to be generally resistant to change during eight hours of exposure at the lower CO concentrations (maximum carboxyhemoglobin saturations of 10 and 22 percent). During the eight hour exposures, the VER was generally resistant to change until COHb levels of 22 percent were achieved, while with 24 hours of exposure changes were evident even at the lowest concentrations (COHb = 4-10 percent). This change, an increase in VER wave amplitude, suggest that these exposures induced central nervous system depression.

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Report No.: CRC APRAC CAPM-3-68-7 MCOW-ENVM-CO-74-3

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Supported by Contract CRC-APRAC, Project No. CAPM-3-68, from the Coordinating Research Council, Inc. and the Environmental Protection Agency.

ABSTRACT

The spontaneous electroencephalogram (EEG) and the visual evoked cortical electrical activity (visual evoked response, VER) were studied in young adult males to ascertain the effects of exposure to carbon monoxide (CO). The EEG was found to be generally resistant to change during; 1) 8 hours of exposure to 50, 100, 200, and 500 parts per million (ppm) CO, and 2) 24 hours of exposure at the lower CO concentrations (maximum carboxyhemoglobin saturations, COHb, = 22 and 10% respectively). During the $\leq$ 8 hour exposures, the VER was generally resistant to change until COHb levels of 22% were achieved, while with 24 hours of exposure changes were evident even at the lowest concentrations (COHb = 4-10%). This change, an increase in VER wave amplitude, suggest that these exposures induced central nervous system depression. Finally, during three hours of exposure (10% COHb) the absence of a general CO effect was still evident when exposure was combined with phenacetin ingestion, benadryl ingestion, or cessation of chronic cigarette smoking. However, there were individual exceptions to these generalizations.

INTRODUCTION

Of major general interest in recent years has been the effect of exposure to carbon monoxide (CO) on physiological systems and behavioral performance. Studies have shown that even low concentrations of CO may exert a detrimental effect on man's capability to perform mental tasks (1-3) and studies on animals have revealed that CO exposure can result in alteration of the visual cortical response evoked by light stimulation of the eye (VER) (4). These concerns and findings provided the impetus for four separate studies completed in our laboratory on the effect of CO exposure on man's VER and spontaneous electroencephalogram (EEG). The specific nature of each study was as follows: In study 1, subjects were exposed at several levels of environmental CO which resulted in carboxyhemoglobin saturation (COHb) ranging from 2-25% (5). In study 2, several subjects were studied more extensively during exposure at the higher levels of CO. Study 3 concentrated on the relevance of duration of exposure and rate of rise of COHb. In study 4, we investigated the possibility of interaction between CO and certain drugs and the effect of acute lowering of COHb in chronic cigarette smokers. In this summary report of our findings, the methodology common to all four studies will be presented followed by a description of each specific protocol and findings, and finally a general discussion on this topic.

GENERAL METHODS

Detailed description of the exposure chamber (6), the analytical methods used to monitor the chamber atmosphere and COHb levels (6, 7) and the arrangement for recording the EEG and VER (5) are contained in previous publications; hence, only the latter (of specific interest) will be presently described.

Electroencephalography - In most experiements gold-plated silver disk electrodes were oriented on the scalp according to the 10-20 International Electrode System. The leads utilized as well as electrode geometry are shown in figure 1. An abbreviated arrangement was utilized in the third study (forehead, inion, and right ear leads). A Grass polygraph fitted with EEG preamplifiers was utilized for recording. In the majority of instances, the EEG was recorded for 15 seconds prior, continuously during, and for 15 seconds after acquisition of the VER. Analysis of the recordings was by visual examination.

Visual Evoked Response

The VER was recorded from the electrode at the inion with the left ear as reference. The amplified VER signal was fed to an on-line averaging computer (Nuclear Chicago, 7100). The VER was triggered by a strobe flash (3 μ sec) at the rate of one per second for 100 seconds. The strobe was operated to

deliver 18 million beam candles at one meter from the subject's eyes which were closed throughout the period of strobe flashing. The analysis period following each flash was 225 milli seconds. Flash delay from the synchronizing pulse which initiated the computer sweep was 25 milli seconds. The computer averaged plot of the responses to 100 stimuli was recorded on X-Y plotter for analysis.

It has been shown that VER amplitude may be altered by varying levels of attention, cortical desynchronization, and sleep (8, 9). Accordingly, an attempt was made to standardize conditions during each exposure day with special attention being given to that period immediately preceding the actual recordings. A rigid schedule of food intake, physical activity, and additional testing procedures was closely adhered to. In additon, after entering the booth, the subject was always allowed 3-5 minutes to achieve a relaxed state, and then immediately prior to initiating the strobe flash, in an attempt to standardize "attention" the subject clapped his hand five times slowly and forcibly.

The most prominent and reproducible portion of the VER complex is the 3rd, 4th and 5th waves (designation by Gastaut) (5, 8, 10). Our analysis was thus directed primarily to these waves. Wave 3 was identified as a positive-going wave which peaked 80-120 milli second after initiation of the strobe flash. Wave 4 and 5 were the succeeding negative and positive deflections and wave 2 (when present) preceded wave 3 as a negative deflection.

Our analysis included: 1) measurement of the amplitude of these waves, and 2) determining whether changes in latency and/or wave form had occurred.

SPECIFIC PROCEDURES AND RESULTS

Study No. 1 - Humans were exposed to CO concentrations of 1, 25, 50, 100, 200, 500 and 1000 ppm for periods ranging from 0.25 to 8 hours. The maximum COHb obtained was approximately 25%. Twelve volunteers healthy male graduate students and two medical school faculty ranging in age from 24-42 years were subjects for this study. The number of subjects exposed at each concentration varied with a minimum of 2 at each level.

Exposure to CO did not induce a characteristic change in any of the subjects' EEG. Presented in Figure 2 are the recordings from one subject after at least 6 hours exposure at 0, 25, 50 and 100 ppm. The highest COHb saturation in these studies was approximately 14%. Figure 3 shows representative recordings from two subjects during control conditions and after achieveing COHb levels in excess of 22%. The EEG appears to be unaltered after exposure to CO.

Changes in the VER were observed only at the highest level of exposure. Eight hours of exposure to low levels of CO (maximum 100 ppm and 14% COHb) did not discernably affect VER wave amplitude latency, or configuration.

However, as shown in Figure 4 COHb levels of 20-25% (500 ppm) resulted in an increase in VER wave amplitude and a negative proceeding shift in the latter VER segments.

Study No. 2 - Eleven young male graduate students were studied on two different days before and after 5 hours of < 2 ppm CO conditions in the chamber and again on two occasions before and after 5 hours exposure to 200 ppm CO. The highest COHb level achieved was 20%. Four of the subjects were also exposed for 5 hours to 50 and 100 ppm CO. No consistent changes in the EEG or VER which could be attributed to CO exposure were detected.

Study No. 3 - Nine young adult males (22-24 years old) served as subjects for this study. Five were studied on ten different days before and at the end of 6 hours in the exposure chamber. The chamber atmosphere during these experiments was as follows: 1) 5 days at < 2 ppm CO; 2) 2 days at 1000 ppm CO initially for 20 minutes and 70 ppm thereafter (1000-70 ppm); 3) 1 day at 1000 ppm CO initially for 20 minutes and 30 ppm thereafter (1000-30 ppm); 4) 30 ppm CO throughout, and 5) 70 ppm CO throughout. The additional four subjects were in the chamber for 6 hours on 4 days, (2 at < 2 ppm and one each at 1000-30 ppm and 1000-70 ppm), and for 24 hours on 6 other occasions (< 2 ppm for 3 days and one each at constant-30 ppm, constant-70 ppm, and 1000-70 ppm). In the 24-hour studies, measurements

were made prior to exposure and after 20 minutes, 6 and 24 hours of exposure. The COHb values were as follows: (1) constant 30 ppm, 1.0% at 30 minutes, 3.0% at 6 hours, and 4.5% at 24 hours, (2) constant 70 ppm, 1.8% at 30 minutes, 5.0% at 6 hours and 10% at 24 hours, (3) 1000-30 ppm, 6% at 6 hours and (4) 1000-70 ppm, 10% at 25 minutes, 6, and 24 hours.

In the analysis of the VER, the mean and SEM of the 2, 3, 4, and 5 wave amplitudes for each subject was determined for < 2 ppm CO conditions. The wave amplitudes on CO exposure days was then compared to these values (figure 5-13). If the amplitude of at least two waves during CO exposure differed from the mean ($\pm$ 2 SEM) during 0 ppm conditions, then it was concluded that CO had induced a change. This method of analysis provided a more objective evaluation of the data. The statistical evaluation of these data supported the results obtained by visual analysis. For example, using the statistical approach as in Figure 5a, one concludes that exposure for 6 hours during 1000-30 and 1000-70 ppm conditions resulted in an increase of VER wave amplitude in subject 37. Visual examination of the actual VER's in Figure 5b leads to the same conclusion. A second example is provided by Figure 8a and 8b. Both figures demonstrate that after 24 hours of exposure during constant -70 and 1000-70 ppm conditions, VER wave amplitude is increased above baseline and above 24 hour < 2 ppm conditions.

During the 24 hour CO exposure study, the major change from < 2 ppm conditions was increased VER wave amplitude after 24 hours of exposure (figures 5-8). This trend was evidenced in 1 of 4 subjects during constant 30 ppm conditions, 3 of 4 at constant 70 ppm conditions and 2 of 4 during 1000-70 ppm conditions. Stated in another manner, subjects #38, 70 and 71 each exhibited increased VER amplitude in two out of the three 24 hour CO exposures. In contrast, no general trends were evident after 20 minutes and 6 hours of CO exposure. The individual exceptions after 20 minutes of exposure were increases in amplitude in subjects 38 and 71 during constant-70 ppm and 1000-70 ppm conditions respectively. After 6 hours of exposure the exceptions were reduced amplitude in subjects 38 and 71 during constant 30 ppm conditions, and increased amplitude in subject #37 during 1000-70 ppm conditions. There were no changes in VER configuration and latency in any subject during any of these conditions. Furthermore, there were no detectable EEG changes during any of the conditions.

During the 6 hour CO exposure studies no major changes were detected in VER wave amplitude, configuration or latency, and the spontaneous EEG. Individual subjects showed VER wave amplitude (Figures 9-13) changes. Subject 37 at 1000-30 ppm and 1000-70 ppm conditions exhibited an increased wave amplitude while subjects 50 and 70 at 1000-70 ppm and subject 69 at constant 30 ppm demonstrated a decrease in wave amplitude.

Study No. 4 - In this exploratory type of study 2 young adult males were monitored on 2 separate days over 3.3 hours during the following conditions: (1) normal chamber atmosphere, < 2 ppm, (2) 1000 ppm in the chamber for 20 minutes and 30 ppm for 3.3 hours (1000-30), (3) 0 ppm CO but ingestion of 10 mg./kg. of the drug phenacetin 15 minutes prior to exposure, (4) 1000-30 ppm CO conditions plus phenacetin (5) 0 ppm CO but ingestion of 50 mg. benadryl (diphenhydramine hydrochloride; Parke Davis) 15 minutes prior to exposure, (6) 1000-30 ppm CO conditions plus benadryl, (7) < 2 ppm CO 2-4 days after cessation of chronic cigarette smoking, and (8) 1000-30 ppm CO conditions 2-4 days after cessation of chronic cigarette smoking. During each of these conditons, EEG and VER measurements were made prior to any treatment and then after 55, 115 and 200 minutes in the chamber.

Two of the above conditions induced changes from normal in the spontaneous EEG. As shown in Figures 14a, b and c, 3.3 hours of 1000-30 ppm CO exposure resulted in an increase in EEG amplitude in subject 151. These changes were not evident after 55 and 115 minutes of exposure. Figures 14d, e and f demonstrate that EEG amplitude in subject 151 was not altered by 3.3 hours of < 2 ppm conditions by 3.3 CO exposure plus phenacetin ingestion, and by phenacetin ingestion alone. In contrast, 3.3 hours of CO exposure alone (Figure 15a), and phenacetin ingestion alone (Figure 15b),

did not alter the EEG amplitude of subject 154, but CO exposure plus phenacetin ingestion did result in an increase in EEG amplitude (figure 15c and d).

None of the conditions of this study induced changes in VER wave amplitude, latency or configuration. Data on wave amplitude is presented in Figures 16-19 (phenacetin 16 and 17, Benadryl 17 and 18, and cessation of cigarette smoking 19).

SUMMARY & COMMENTS

The information obtained regarding the effect of CO exposure on the spontaneous EEG and the VER can be summarized as follows: First, exposure for 8 hours to an environment containing up to 500 ppm CO (maximum COHb = 25%) does not induce any major, general changes in the spontaneous EEG. Furthermore, exposure for 24 hours to CO concentrations that gradually increase COHb levels to 10% or rapidly increase COHb to a constant level of 10% do not result in major EEG alterations. However, one individual exception was observed during CO exposure alone and a second when CO exposure was combined with ingestion of phenacetin (increased amplitude). Second, CO exposure for 8 hours to concentrations that increase COHb to approximately 16% does not induce any major alteration in VER wave amplitude, latency or configuration. However, a small percentage of subjects do demonstrate some

changes in wave amplitude. Third, CO exposure for 8 hours at concentrations increasing COHb to above 22% results in an increase in VER wave amplitude. Fourth, exposures to CO for 24 hours (COHb $\leq$ 10%) will in a majority of subjects increase the amplitude of the VER. Fifth, over a limited range (COHb up to 10%) the rate of rise of COHb is not of importance regarding potential effects on the VER. Finally, phenacetin and benadryl alone and in combination with CO and cessation of cigarette smoking alone and combined with CO exposure do not induce any changes in VER wave amplitude, latency, or configuration.

Exposure to high levels of CO for short periods (COHb > 20% for < than 8 hours) and to low levels for longer periods (< 10% for 24 hours) results in an increase in VER wave amplitude. It is thought that these changes would be consistent with mild to moderate central nervous system depression. The consequence of such depression on adult males' mental and physical performance capacity is largely unknown, but our findings suggest that performance on specific-isolated tasks is not altered (7). In this respect it is of interest though that firemen and chronic heavy smokers achieve COHb levels in their normal lives which in our experimental condition induced changes in the VER.

Further studies should be conducted in at least two areas. First, because one of two subject's EEG wave amplitude increased when CO exposure was combined with phenacetin ingestion, further studies should be conducted

to elicit the potential interaction effects of CO and drugs. Second, because 24 hours of exposure induced VER changes at COHb levels eliciting no effects after shorter exposures, longer exposure of exposure should be studied to ascertain whether the change is sustained, whether it progresses, or whether there is adaptation to CO exposure.

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FIGURES

1. From Figure 1 of reference 5. It demonstrates EEG and VER electrode position and geometry utilized for most of our studies. The recording is typical of spontaneous EEG activity of subjects in study No. 1.

2. From Figure 2 of reference 5. Presented are EEG recordings of one subject after 6 hours exposure to indicated levels of environmental CO.

3. From Figure 4 of reference 5. Presented are EEG recordings of two subjects after 6 hours exposure to relatively high levels of environmental CO.

4. From Figure 6 of reference 5. Presented are VER recordings from 2 subjects after 6 hours exposure to relatively high levels of environmental CO.

5a. VER wave amplitude of subject 37 during 24 and 6 hour studies in the third investigation of our series. The bar graphs represent the mean ($\pm$ 2 SEM) wave amplitude during $<$ 2 ppm conditions. The individual symbols represent wave amplitude during CO exposure as follows: 1) 24 hour study - 0 = 30 ppm CO throughout, Δ = 70 ppm CO throughout, and ● = 1000 ppm CO for 20 minutes and 70 ppm for remainder of study (1000-70 ppm conditions), and 2) 6 hour study - ▲ = 1000 ppm CO for 20 minutes and 30 ppm for remainder of study (1000-30 ppm conditions), and ■ = 1000 - 70 ppm conditions.

5b. Actual VER recordings of subject 37 during various conditions. On 7/11/72 and 8/1/72, six hour studies were completed during 1000 - 30 and 1000 - 70 ppm conditions respectively. On 7/12/72, 7/13/72, and 7/26, 27/72, 24-hour studies were completed during < 2 and 1000 - 70 ppm conditions respectively. Analysis by visual examination of the actual recordings in this figure, generally leads to the same conclusions obtained by analysis via the statistical approach (figure 5a).

6. VER wave amplitude of subject 38 during 24- and 6-hour studies in the third investigation of our series. The data is presented as described in legend for Figure 5a.

7. VER wave amplitude of subject 70 during 24- and 6-hour studies in the third investigation of our series. The data is presented as described in legend for figure 5a.

8a. VER wave amplitude of subject 71 during 24- and 6-hour studies in the third investigation of our series. The data is presented as described in legend for Figure 5a.

8b. Actual VER recordings of subject 71 during various conditions. All recordings were from 24 hour studies (7/26, 27/72 = 1000 - 70 ppm conditions, 8/7, 8/72 = < 2 ppm conditions, and 8/9, 10/72 = constant 70 ppm conditions). Analysis by visual examination of the actual recordings on this figure generally leads to the same conclusion obtained by analysis via the statistical approach (Figure 8a).

9. VER wave amplitude of subject 50 during 6 hour studies in the third investigation of our series. The data is presented as described in legend for Figure 5a with individual symbols the same as in the 24-hour study.

10. VER wave amplitude of subject 55 during 6 hour studies in the third investigation of our series. The data is presented as described in legend for Figure 5a with individual symbols the same as in the 24-hour study.

11. VER wave amplitude of subject 67 during 6 hour studies in the third investigation of our series. The data is presented as described in legend for Figure 5a with individual symbols the same as in the 24-hour study.

12. VER wave amplitude of subject 68 during 6 hour studies in the third investigation of our series. The data is presented as described in legend for Figure 5a with individual symbols the same as in the 24-hour study.

13. VER wave amplitude of subject 69 during 6 hour studies in the third investigation of our series. The data is presented as described in legend for Figure 5a with individual symbols the same as in the 24-hour study.

14 a, b, and c. Sample EEG tracings from subject 151 on 3 days during baseline conditions and after 3 hours exposure to 1000-30 ppm CO exposure conditions (COHb = constant 15%).

14 d, e, and f. Sample EEG tracings from subject 151 during baseline conditions and after 3 hours of the following conditions: < 2 ppm CO exposure, ingestion of 10 mg./kg. of phenacetin, and phenacetin ingestion plus 1000-30 ppm CO exposure.

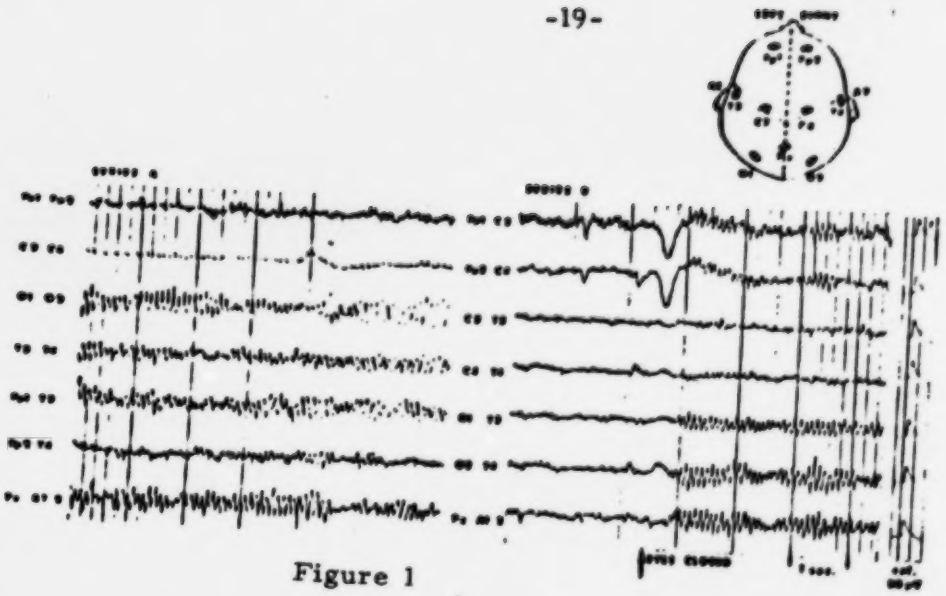
15 a, b, c, d. Sample EEG tracing from subject 154 on 4 days during baseline conditions and after 3 hours of the following condition: 1000-30 ppm CO exposure alone (15a), phenacetin ingestion alone (15b), and 1000-30 ppm CO exposure plus phenacetin ingestion (15 c and d).

16. VER wave amplitude of subject 151 during various conditions in the fourth investigation of our series. Bar graphs represent the mean (± SEM) amplitude of data obtained on two separate days.

17. VER wave amplitude of subject 154 during various conditions in the fourth investigation of our series. Bar graphs represent the mean (± SEM) amplitude of data obtained on two separate days.

18. VER wave amplitude of subject 155 during various conditions in the fourth investigation of our series. Bar graphs represent the mean (±SEM) amplitude of data obtained on two separate days.

19. VER wave amplitude of subjects 151 and 130 during one phase of the fourth investigation of our series. Bar graphs represent the mean (±SEM) amplitude of data obtained on two separate days. During normal cigarette smoking and during the period of no smoking, measurements were made during baseline conditions (low COHb) and after 3 hours exposure to 1000-30 ppm CO conditions (high COHb).



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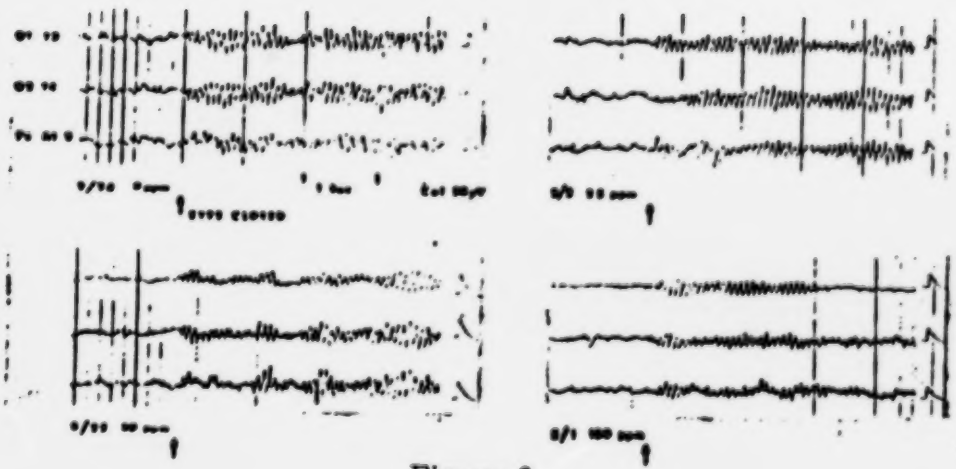
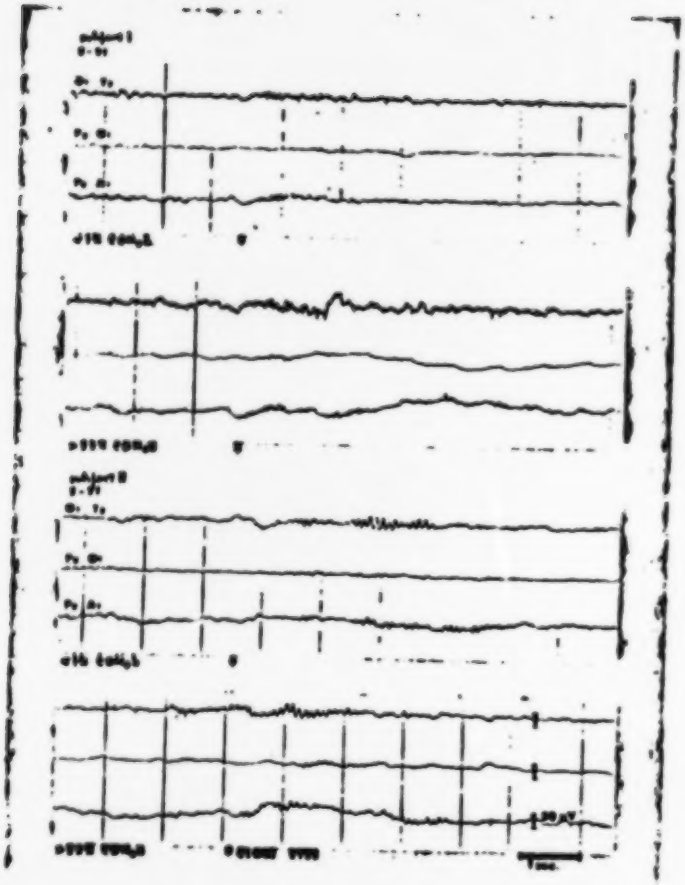


Figure 2



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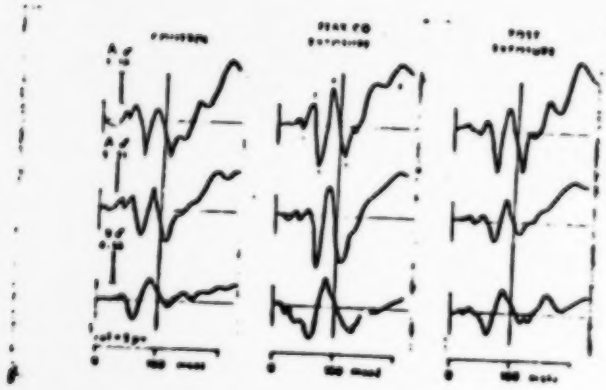

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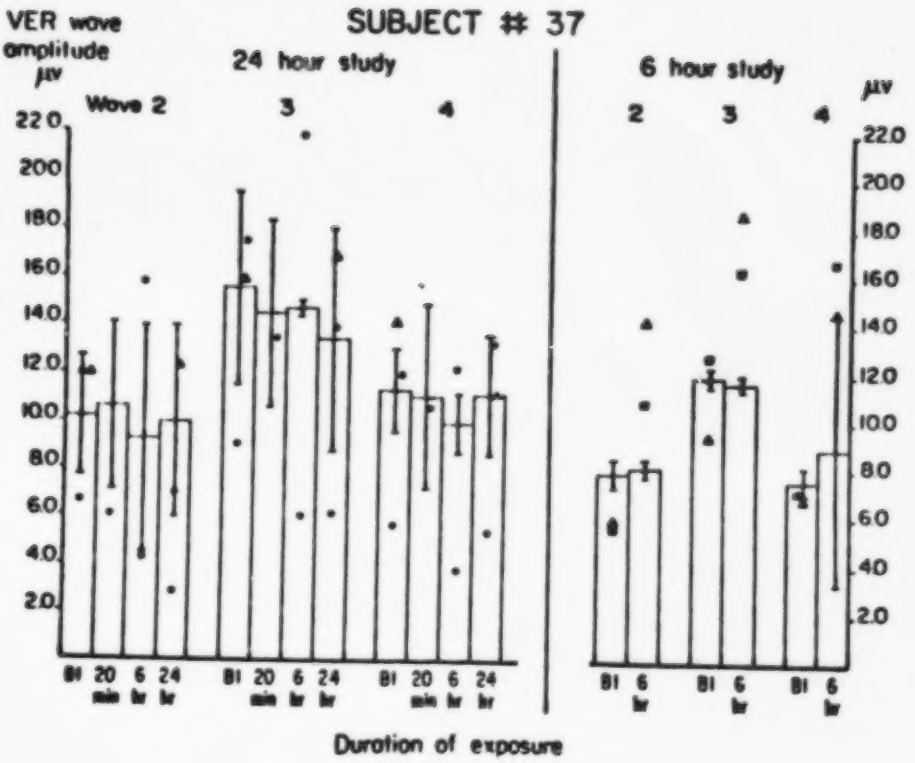


Figure 5a

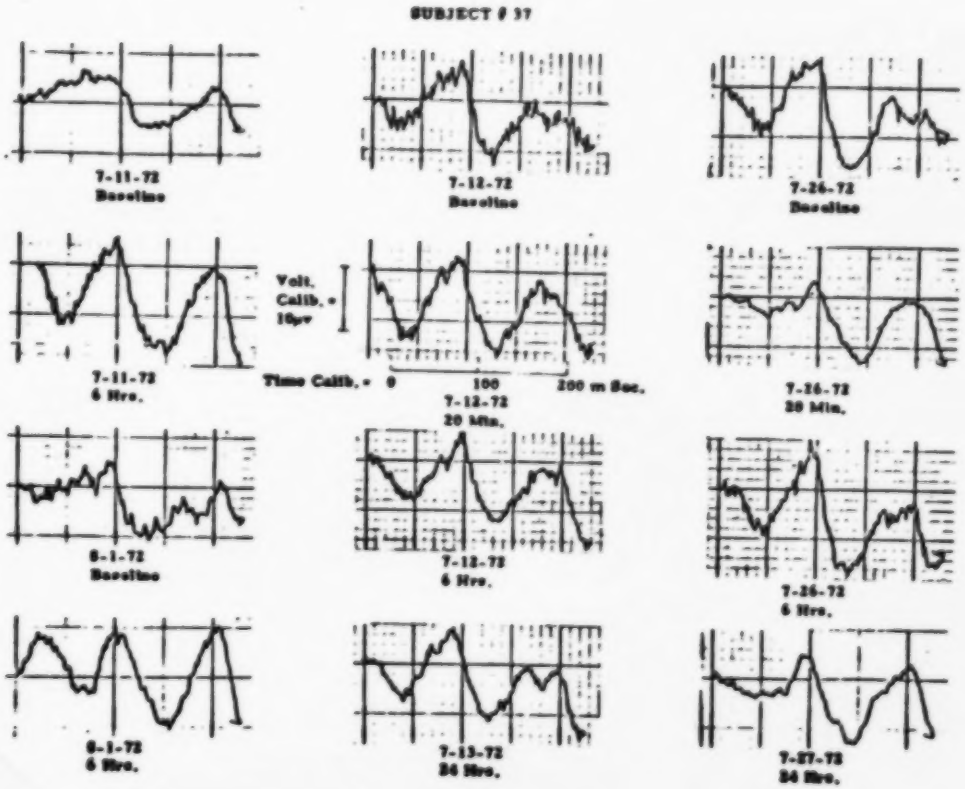
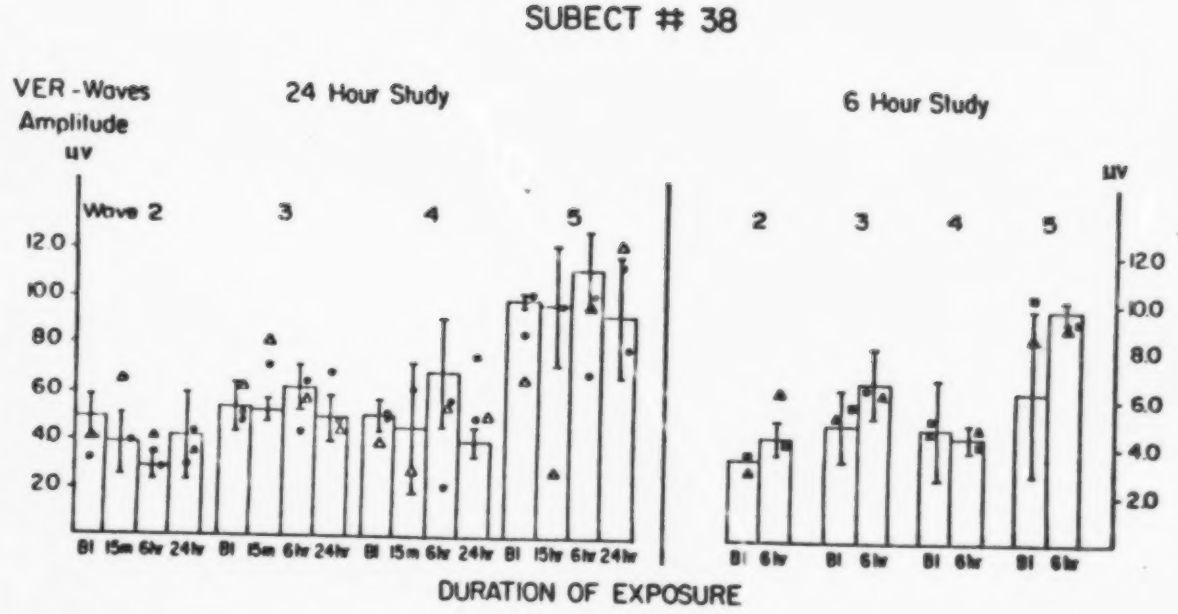


Figure 5b



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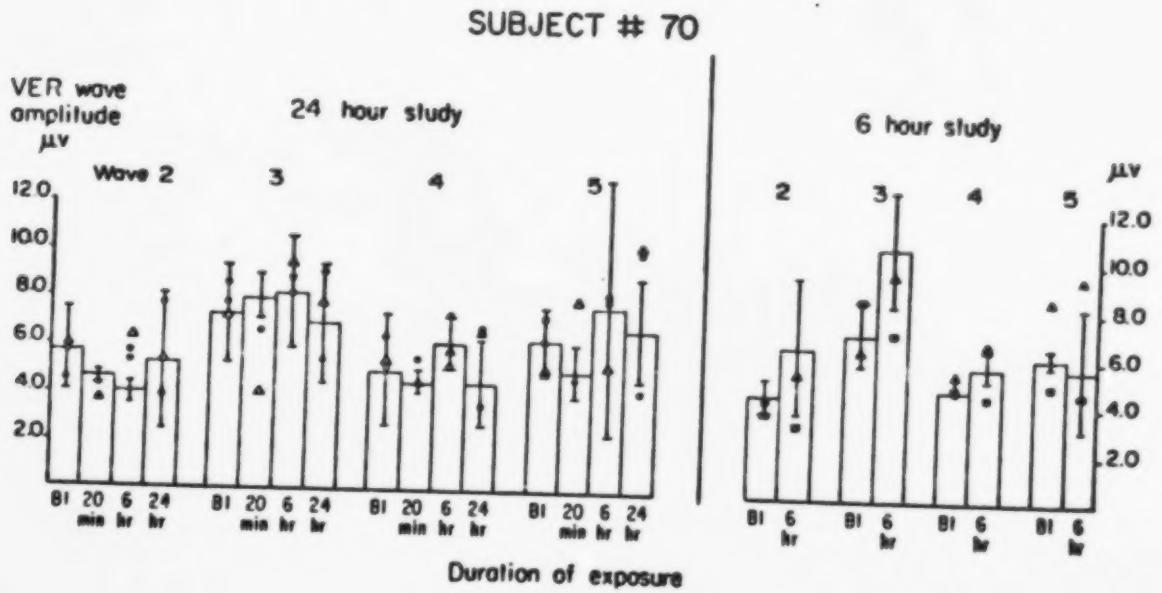

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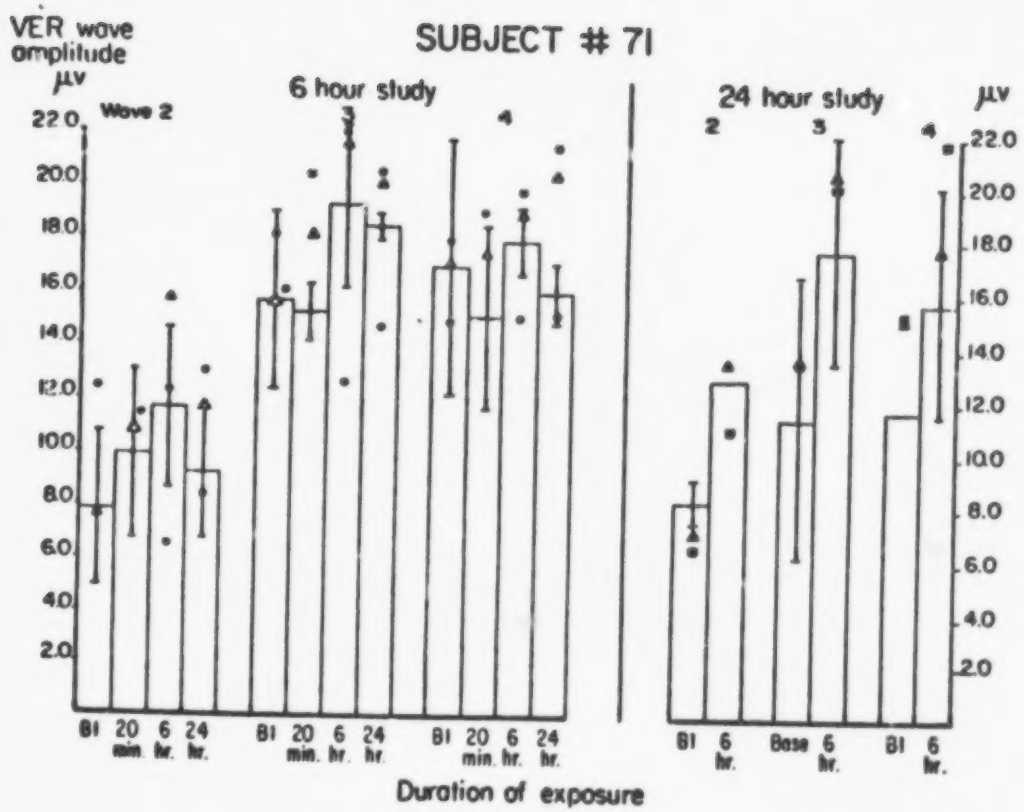

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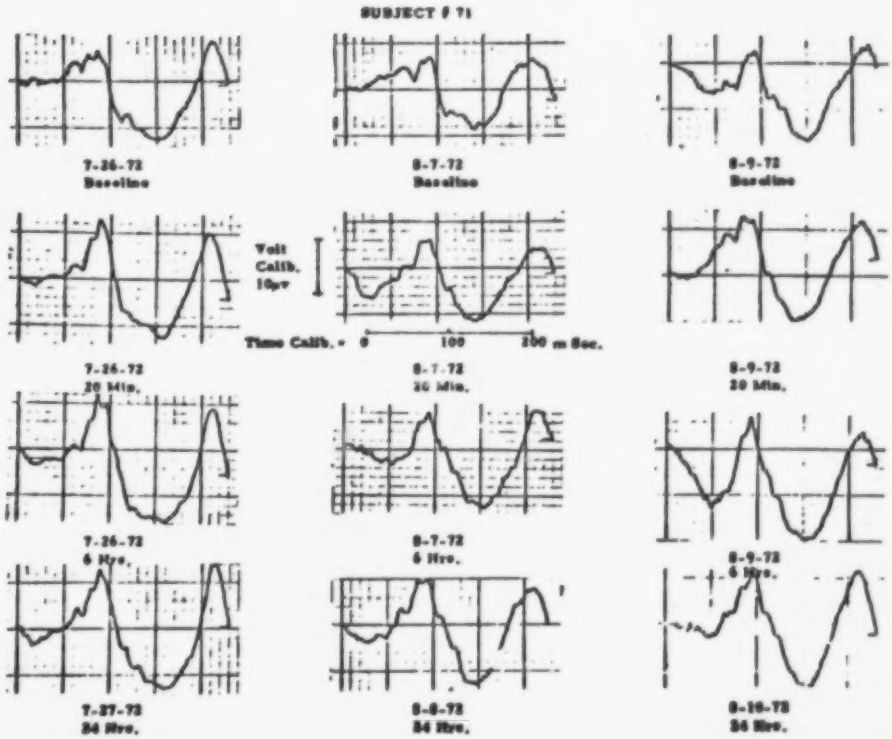
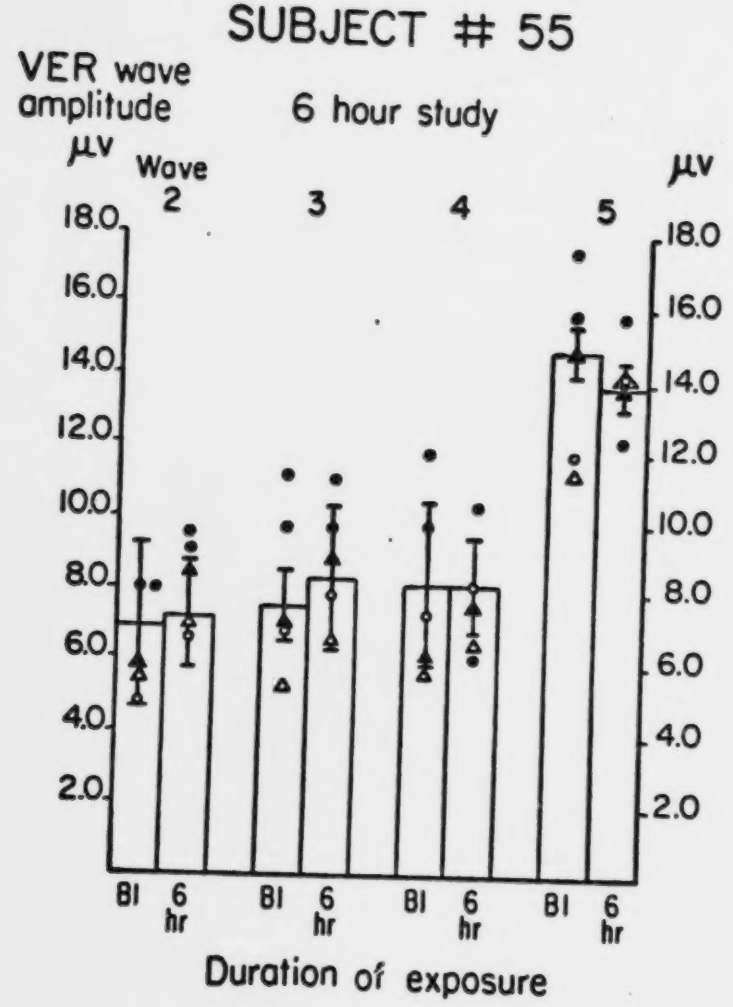


Figure 8b



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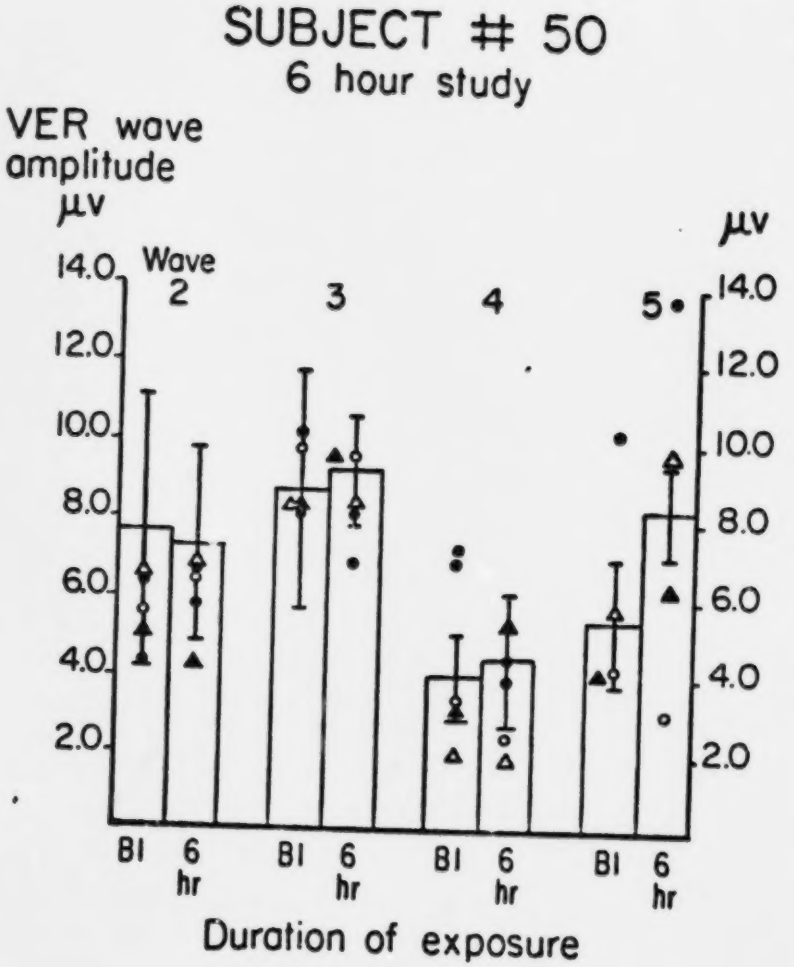

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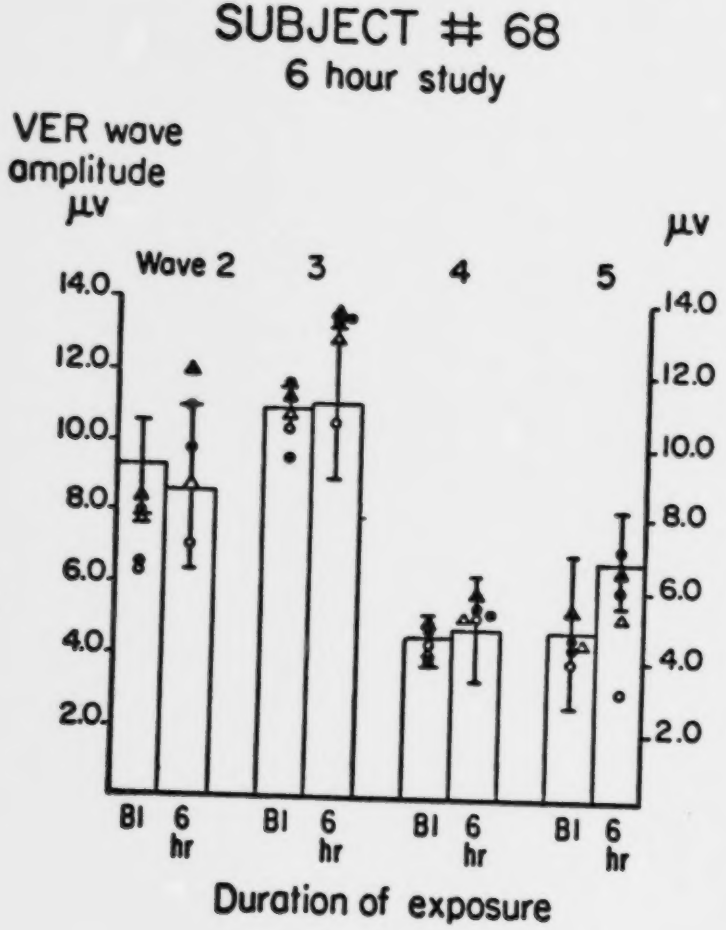

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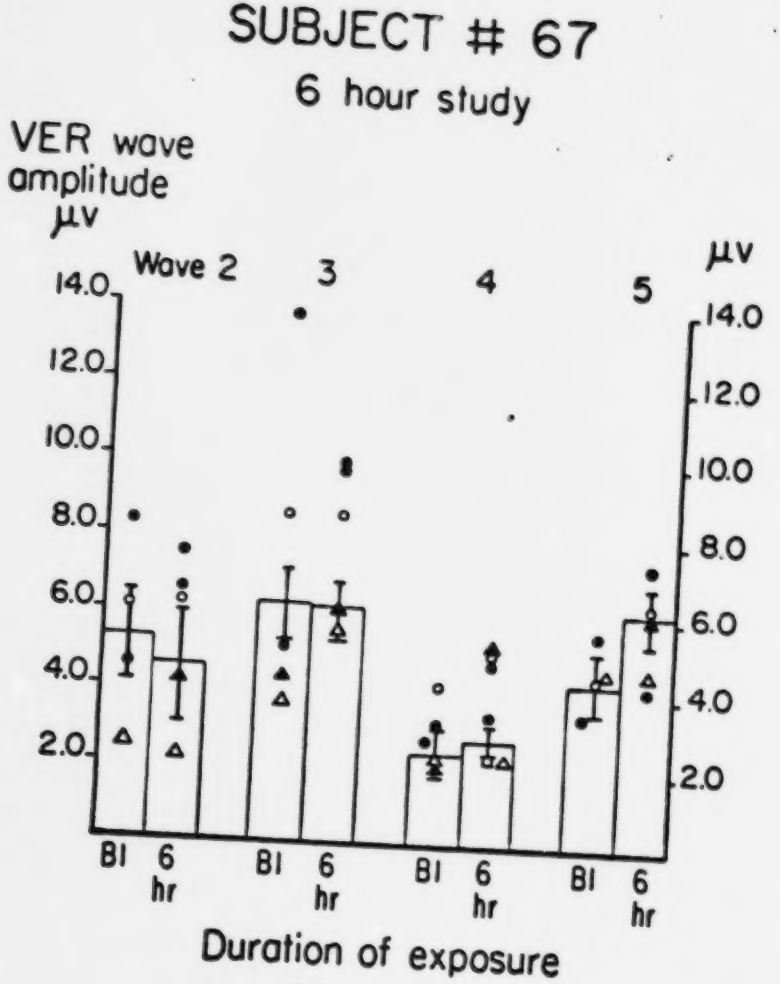


Figure 11

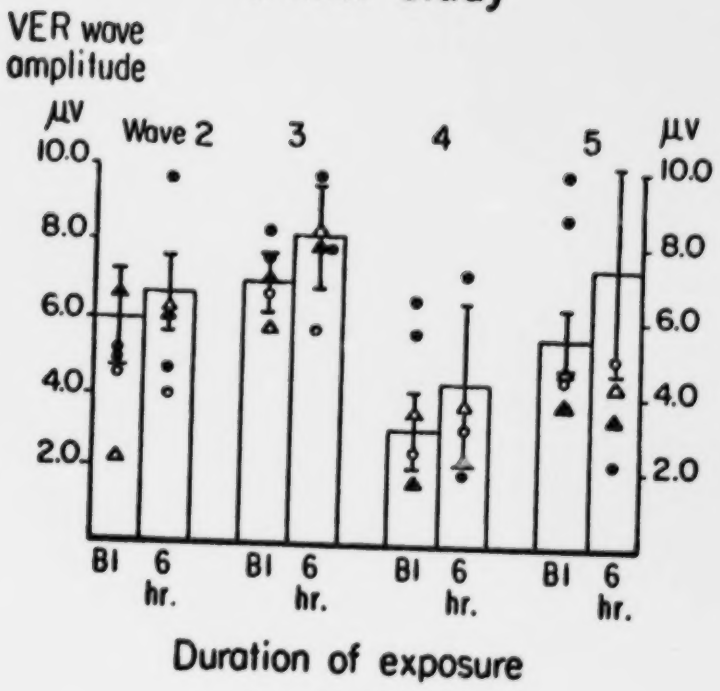

SUBJECT # 69
6 hour study
VER wave amplitude
μV
Wave 2
3
4
5
μV
10.0
8.0
6.0
4.0
2.0
Bl
6 hr.
Duration of exposure

Figure 13

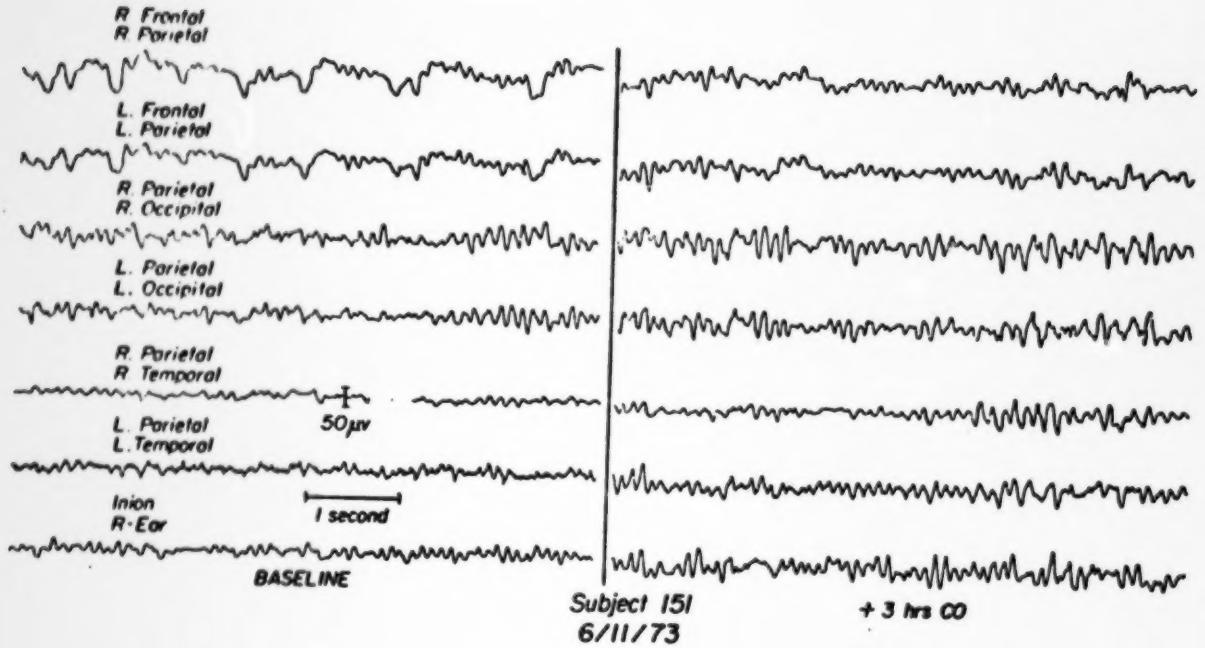


Figure 14a

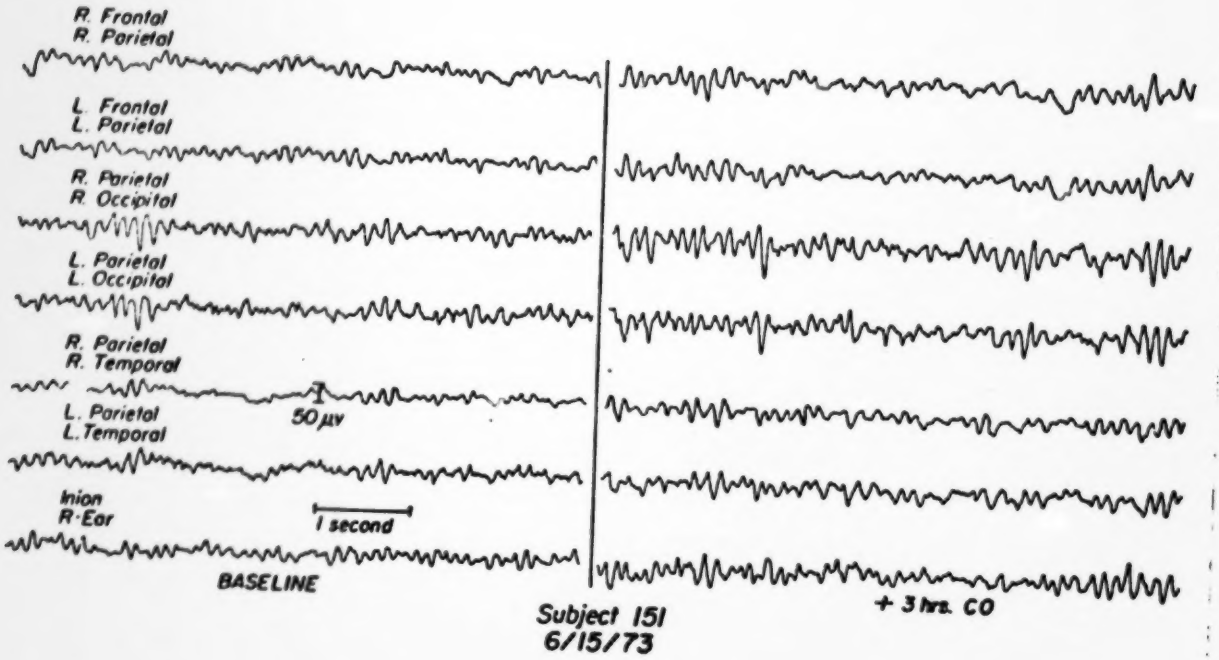
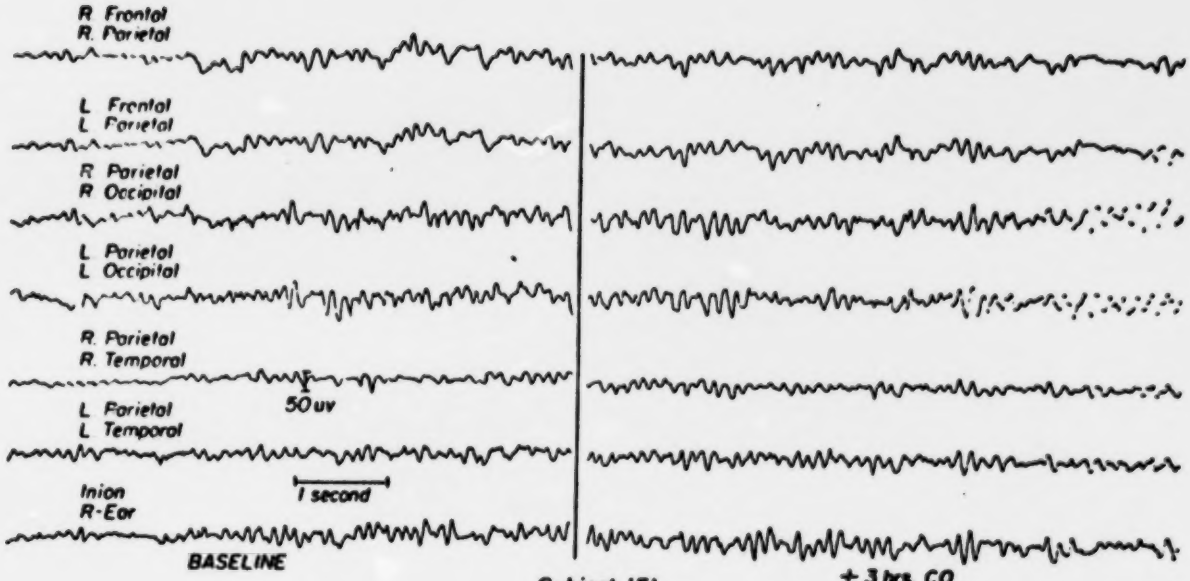
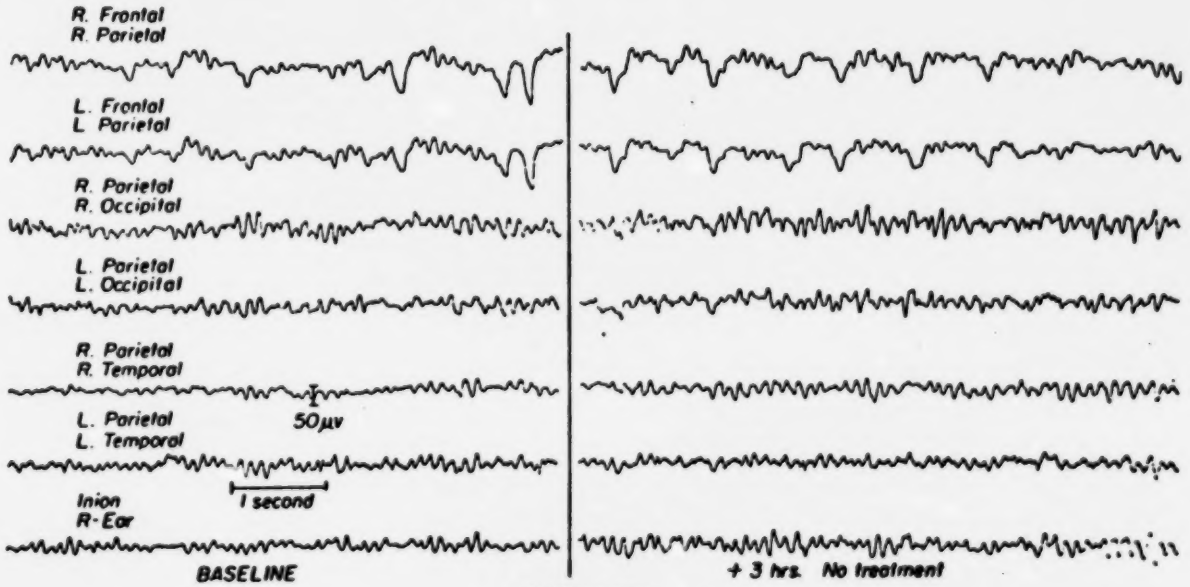


Figure 14b



Subject 151
6/18/73

Figure 14c



Subject 151
5/31/73

Figure 14d

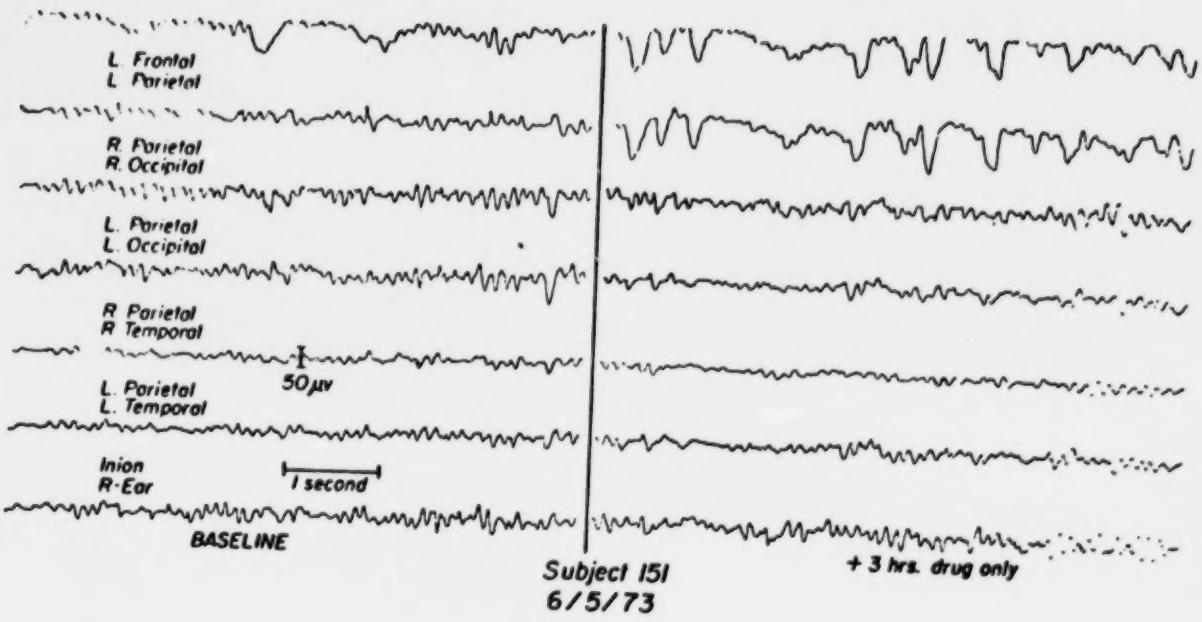


Figure 14e

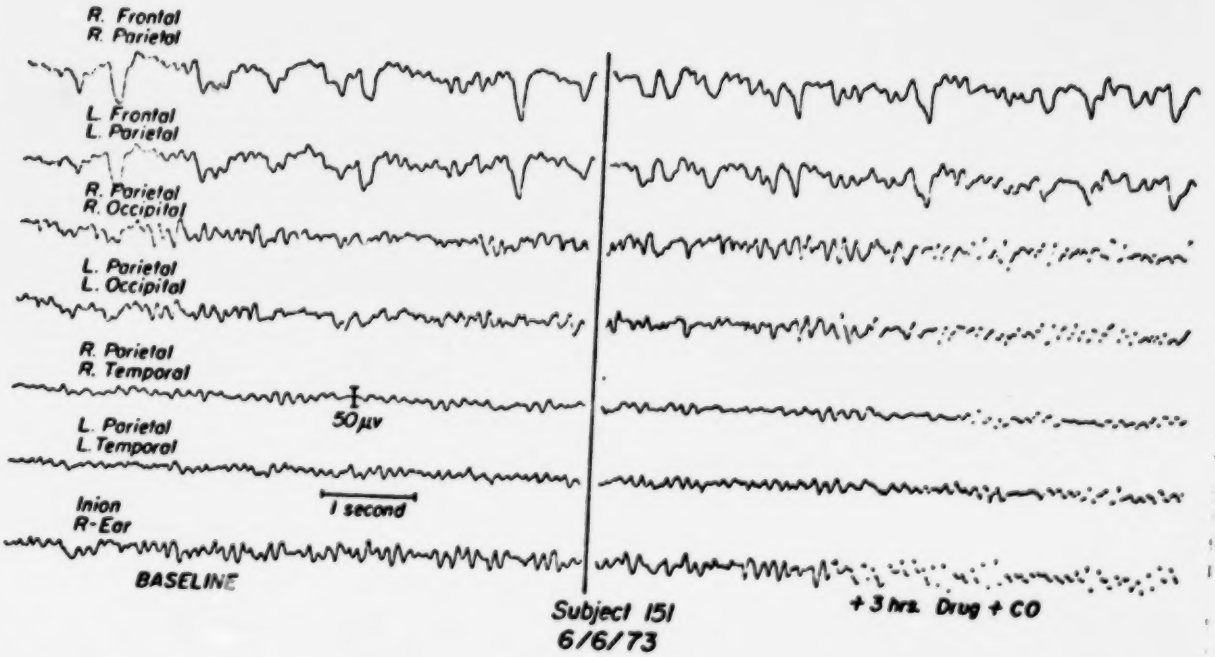


Figure 14f

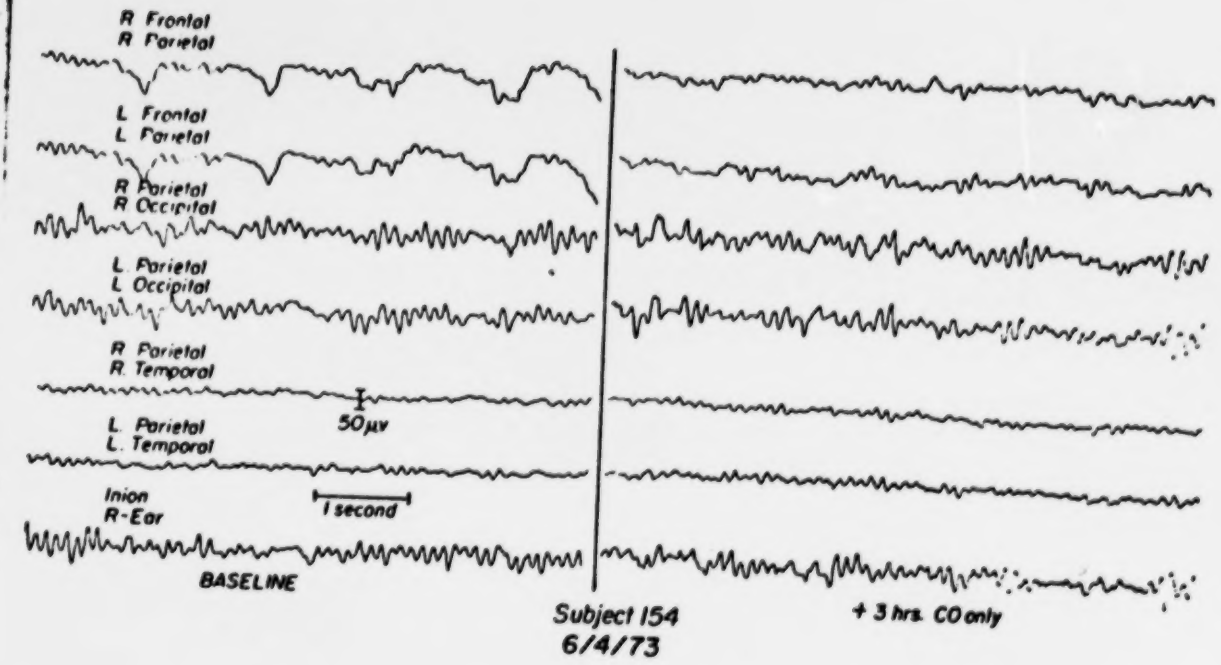


Figure 15a

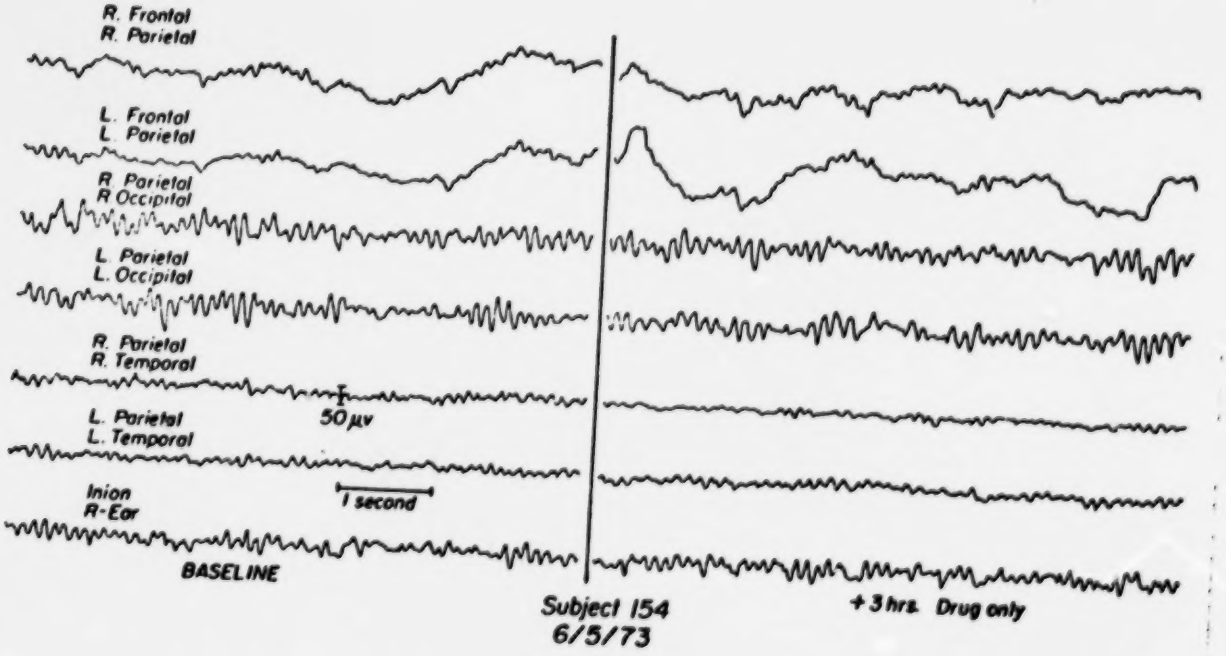
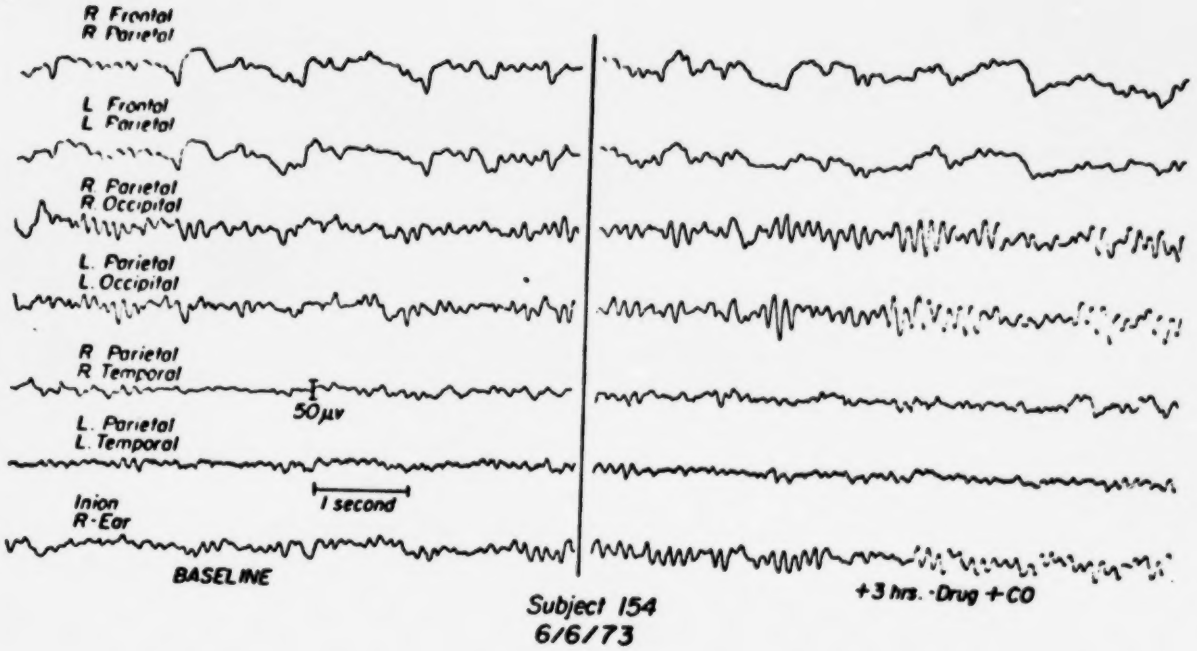
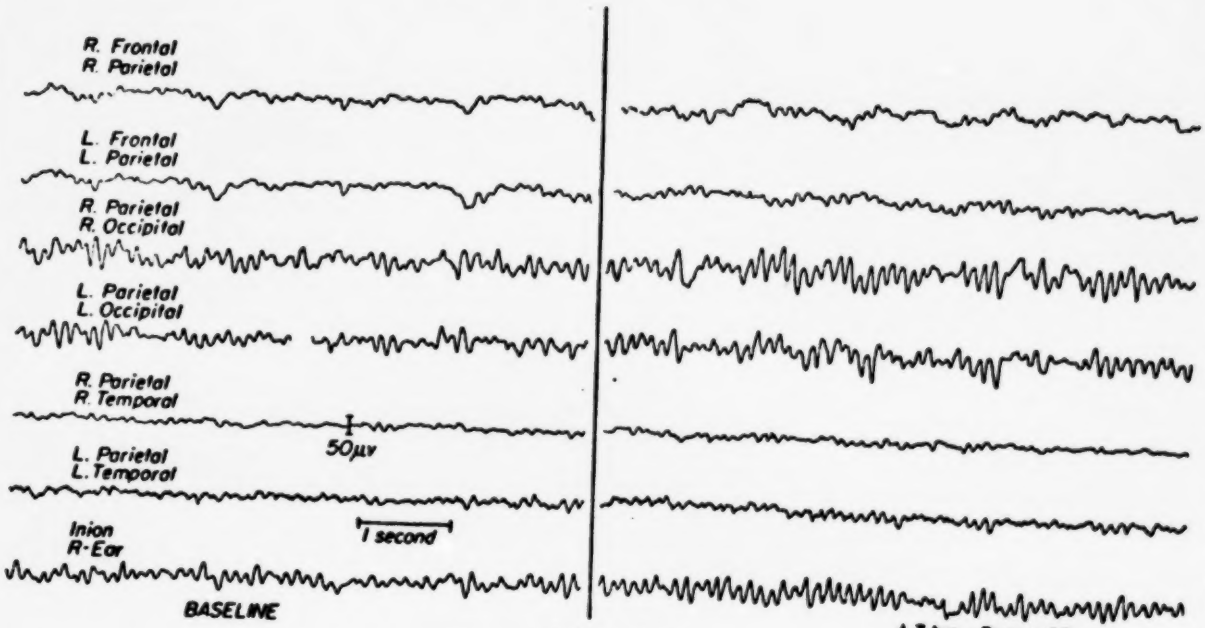


Figure 15b



Subject 154
6/6/73

Figure 15c



Subject 154
6/8/73

Figure 15d

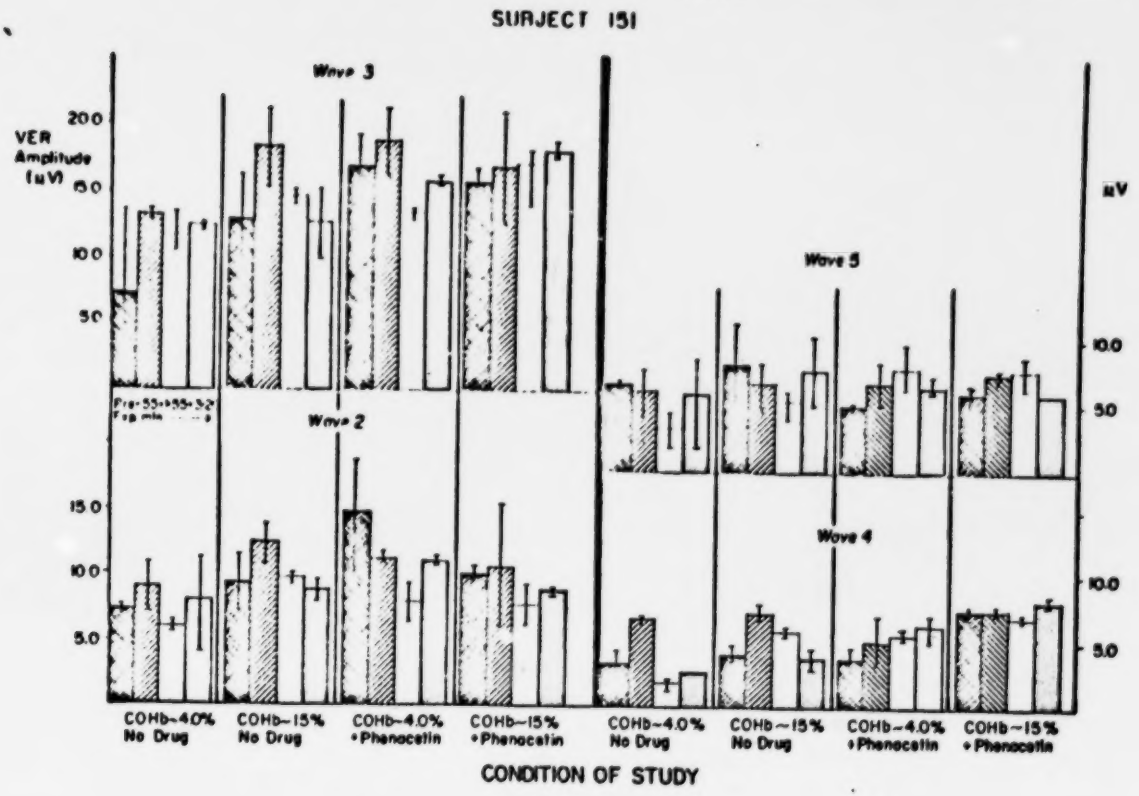


Figure 16

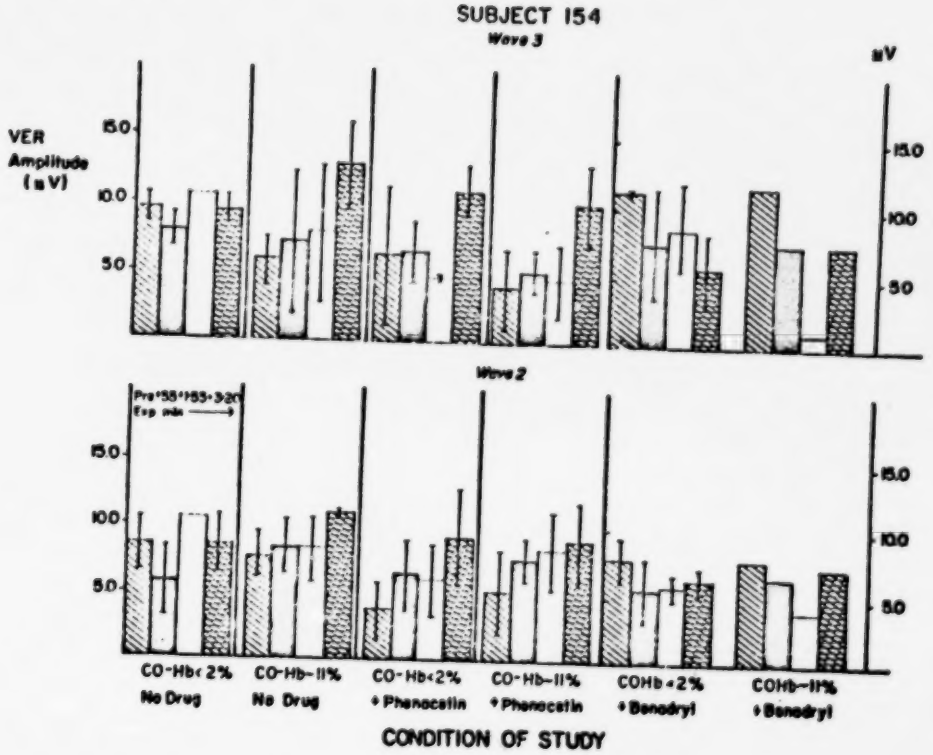


Figure 17

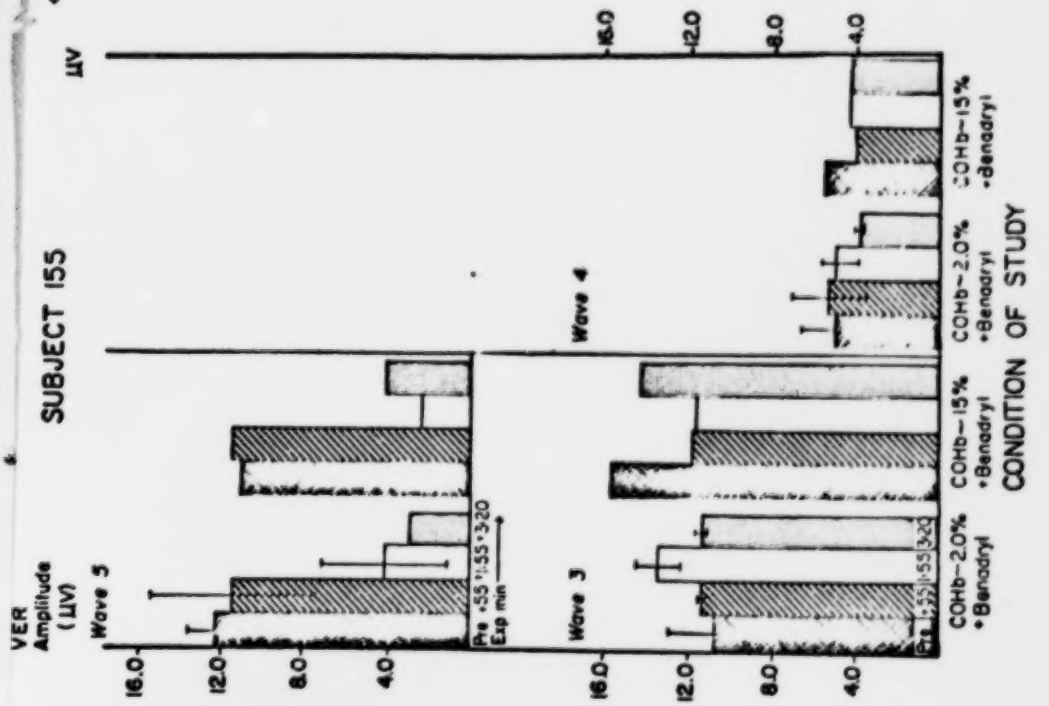


Figure 18

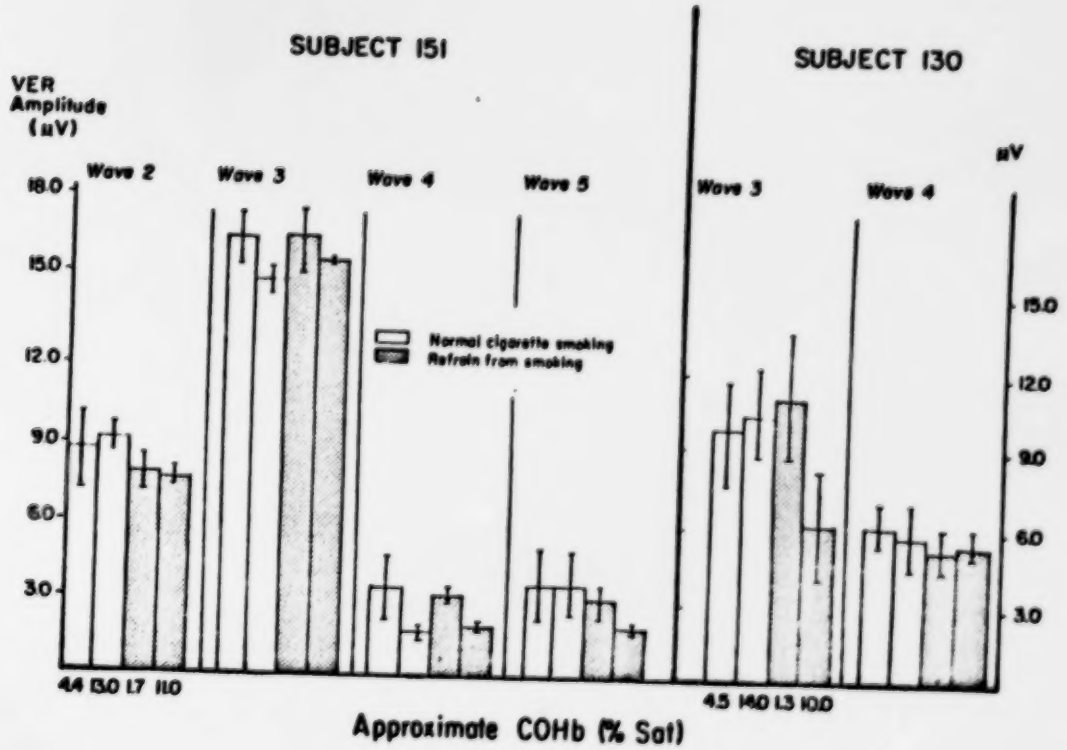


Figure 19